UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs, v. TORRENT PHARMACEUTICALS LTD. and TORRENT PHARMA INC., Defendants.	Civil Action No. 17-3186 (SRC)(CLW) (CONSOLIDATED) (Filed Electronically)
TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs, v. INDOCO REMEDIES LTD., Defendant.	Civil Action No. 17-7301 (SRC)(CLW) (Filed Electronically)

TAKEDA'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT AND VALIDITY

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OTHER AUTHORITIES

GLOSSARY OF TERMS

The ’051 patent	U.S. Patent No. 5,142,051
The ’344 patent	U.S. Patent No. 7,723,344
The ’476 patent	U.S. Patent No. 5,780,476
Aertgeerts	Aertgeerts, K., et al., “Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation,” 13(2) Protein Sci. 412-421 (Feb. 2004)
ANDA	Abbreviated New Drug Application
Berge	Berge, S.M., et al., Pharmaceutical Salts, 66(1) J. Pharm. Sci., 1-19 (Jan. 1977)
CA ’730 patent	Canadian Patent 2,435,730
Campbell	Campbell, D.B., Stereoselectivity in Clinical Pharmacokinetics and Drug Development, 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990)
Crossley	Crossley, R., Chirality and the Biological Activity of Drugs, CRC Press (1995)
Davies	Davies, T.G., et al., “Structure-based design of cyclin-dependent kinase inhibitors,” 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002)
DCAX	1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine.
Defendants	Torrent and Indoco
DPP-IV	dipeptidyl peptidase-4
Engel	Engel, M., et al., “The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism,” 100(9) PNAS 5063-068 (Apr. 29, 2003)
Evans	Evans, D., “Dipeptidyl peptidase IV inhibitors,” 5(6) IDrugs 577-585 (June 2002)
FDA	U.S. Food and Drug Administration
Higgins	Higgins, J.D. & Rocco, W.L., Pharmaceutical Preformulation, Today’s Chemist at Work 22-26 (July 2003)
Hutt	Hutt, A.J., The Development of Single-Isomer Molecules: Why and How, 7(4 supp. 1) CNS Spect. 14-22 (2002)
Indoco	Defendant Indoco Remedies Ltd.
Izumi	Izumi, T., et al., “Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data,” 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997)

Kim 1998	Kim *et al.*, "Anti-diabetic Activity of Constituents of Lycii Fructose," The Journal of Applied Pharmacology, Vol. 6, pp. 378-82 (1998)
Lambeir	Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV," 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003)
Methyl butenyl group	3-methyl-2-buten-1-yl
Plaintiffs or Takeda	Plaintiffs Takeda Pharmaceutical Company, Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Limited
POSA	Person of Ordinary Skill in the Art
PTO	U.S. Patent and Trademark Office
Salt References	The Berge and Higgins References
SMF	Statement of Material Facts
Stereoisomer References	The Campbell, Hutt, Crossley, and Izumi references
Structure References	The Evans, Wiedeman, Lambeir, Engel, and Aertgeerts references
Substitution References	The '051 patent, the '476 patent, and Davies references
Torrent	Defendants Torrent Pharmaceuticals, Ltd. and Torrent Pharma Inc.
Wiedeman	Wiedeman, P., et al., "Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes," 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003)
WO '496 publication	International Patent publication WO 2003/004496

I. INTRODUCTION

Takeda owns and has the right to enforce U.S. Patent No. 7,807,689 ("the '689 patent"), which is directed to Alogliptin – a new chemical entity developed by Takeda that is effective in treating type-2 diabetes. Alogliptin is an active ingredient in three diabetes medications marketed and sold by Takeda. The Defendants have submitted ANDAs asking FDA to approve their respective generic copies of Takeda's products before the '689 patent expires. This is an act of infringement under the Hatch Waxman Act, 35 U.S.C. § 271, and Defendants have stipulated to this infringement. Takeda respectfully moves for summary judgment that (i) Defendants' generic Alogliptin products, if allowed on the market, would infringe claims 4 and 12 of Takeda's '689 patent; and (ii) claims 4 and 12 of the '689 patent are not invalid. Claims 4 and 12 of the '689 patent recite the chemical structure of Alogliptin and its benzoate salt. Takeda intends to move forward in this litigation only on these two claims. Accordingly, if the Court grants summary judgment in favor of Takeda, there will be no need for trial.

Both Torrent and Indoco have stipulated that their proposed generic Alogliptin products meet every limitation of each asserted claim, and therefore infringe. (*See* SMF ¶¶ 39-40.) To succeed in this litigation, therefore, Defendants must prove by clear and convincing evidence that Takeda's compound patent is invalid. The ***only*** theory Defendants offer, through their experts Drs. Ferraris and Rotella, is that the inventions of the '689 patent would have been obvious to a POSA based on combinations of prior art references cobbled together by Defendants that they claim invalidate the '689 patent under either 35 U.S.C. § 103 (Ferraris) and/or the judicially created doctrine of obviousness-type double patenting (Rotella). (*Id.* ¶ 41.) This type of challenge is extraordinary, as obviousness attacks directed to compound patents covering new chemical entities are routinely rejected. *See*, *e.g.*, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) (affirming summary judgment of validity of rabeprazole); *Yamanouchi Pharm.*

Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000) (affirming JMOL in favor of validity of famotidine); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) (affirming judgment of nonobviousness of aripiprazole over § 103 and obviousness-type double patenting arguments).[1]

Indeed, Takeda has found only ***one case*** in the history of Hatch-Waxman jurisprudence (35 years) that has ever affirmed a determination of obviousness for a patent claiming a new chemical entity. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 769 F.3d 1339, 1345-6 (Fed. Cir. 2014) (finding compound patent obvious where, unlike here, the patent owner admitted that the lead compound in question was actually being used as such at the relevant time and required only "conservative changes" to arrive at the patented compound). None of the arguments advanced by Defendants suggest that this case should become the second.

Defendants' obviousness theories are built upon hindsight and fanciful reverse engineering, neither of which is sufficient to satisfy their burden of proof by clear and convincing evidence, nor even to justify a trial. Both defense experts begin their obviousness analyses with compounds that are dramatically different from Alogliptin. In fact, they would require at least ***six*** chemical changes (or more) to get from Defendants' starting compounds to Alogliptin, and no POSA would be motivated to make ***any*** of these changes, much less all of them, nor have any expectation of success in doing so. To the contrary, the very art cited by Defendants, and the common knowledge of a POSA, taught away from such changes. Like the defendants in *Shire LLC v. Amneal Pharms., LLC*, Civ. No. 11-3781 SRC, 2014 WL 2861430 (D.N.J. June 23, 2014), *aff'd in relevant part*, 802 F.3d 1301 (Fed. Cir. 2015), Torrent and Indoco attempt to weave an

[1] Four other generic companies that filed ANDAs seeking approval to make copies of one or more of Takeda's Alogliptin products did not contest the validity of the '689 patent. Instead, they asked FDA to approve their generic products only after the '689 patent expires.

obviousness story that is anything but obvious; it is instead hopelessly complex, involving starting compounds no one would choose and multiple, subsequent chemical changes no one would make. Just as it did in *Shire*, this Court should respect the statutory presumption of validity accorded to Takeda's '689 patent, and should grant summary judgment that the patent is valid and enforceable.

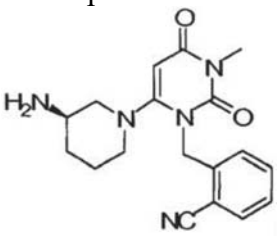
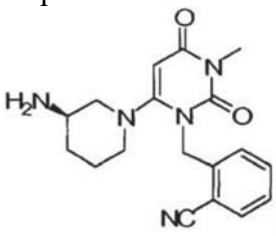
II. FACTUAL OVERVIEW

This action concerns Defendants' applications to make and market generic copies of Takeda's patented products (Nesina®, Kazano®, and Oseni®) prior to the expiration of Takeda's asserted patents. (SMF ¶¶ 24-33.) Takeda's products all contain Alogliptin as an active ingredient,[2] and all are effective in treating type-2 diabetes. (*Id.* ¶ 12.) Specifically, Takeda's Alogliptin products work to inhibit the activity of an enzyme that regulates sugar uptake, known as DPP-IV. (*Id.*) In granting approval, FDA recognized Alogliptin as a new chemical entity that had not been used previously in any FDA-approved drug. (*Id.* ¶¶ 13.)

A. Takeda's '689 Patent Covers the Alogliptin Compound and its Benzoate Salt

Takeda owns several patents that cover its Alogliptin products, including the '689 patent, and has listed them in FDA's Orange Book. (*Id.* ¶ 10.) The '689 patent expires June 27, 2028. (*Id.* ¶ 11.) Claims 4 and 12 of the '689 patent are so-called "picture claims" that describe and claim the very chemical structure of Alogliptin (claim 4) and its benzoate salt (claim 12), as shown below. (*Id.* ¶¶ 8-9.) In allowing these claims, the PTO recognized that the inventions described were novel and neither anticipated by, nor obvious in view of, the prior art.

[2] Alogliptin is the only active ingredient in Nesina®, while Kazano® and Oseni® are combination products that include both Alogliptin and a second active ingredient (metformin and pioglitazone, respectively). (*Id.* ¶ 23.)

4. A compound of the formula  or pharmaceutically acceptable salts thereof.	12. A compound of the formula  wherein the compound is present as a benzoate salt.

B. Defendants Filed ANDAs For Infringing Products

Torrent submitted to FDA ANDA Nos. 21-0159, 21-0160, and 21-0161, which seek approval of Torrent's proposed generic versions of Nesina®, Kazano®, and Oseni®, respectively. (*Id.* ¶¶ 25-29.) Similarly, Indoco submitted to FDA ANDA Nos. 210002 and 20998, which seek approval of Indoco's proposed generic versions of Nesina® and Kazano®, respectively. (*Id.* ¶¶ 30-33.) Both Torrent and Indoco included in their ANDAs a so-called "Paragraph IV Certification" directed to the '689 patent, asserting that their proposed generic products would not infringe the patent and/or that the patent is invalid. (*Id.* ¶ 25-33.) Accordingly, Torrent and Indoco both asked FDA to approve their generic products before the expiration of the '689 patent. Again, Defendants subsequently stipulated to infringement in this case. (*Id.* ¶¶ 39-40.)

C. This Litigation Was Timely Filed By Takeda, And The Only Issue Before the Court Relating To The '689 Patent Is Defendants' Obviousness Challenge.

Within 45 days of receiving notice from Torrent and Indoco regarding the filing of their ANDAs, Takeda filed suit under the Hatch-Waxman Act, asserting infringement of several patents that cover Takeda's Alogliptin products, including the '689 patent. (*Id.* ¶¶ 34-36.) The Court consolidated the Torrent and Indoco actions for all purposes. (*Id.* ¶ 38.) The parties exchanged written and document discovery, but agreed that fact depositions were unnecessary in this case, especially since infringement is not contested. The parties agree that the only issues remaining in the litigation are Defendants' invalidity arguments, as set forth in the reports of their experts, Drs.

Dana Ferraris and David Rotella, dated June 14, 2019 (opening) and August 23, 2019 (reply). (*Id.*, Exs. 11-14.) Takeda has one expert, Dr. David Nichols, and his report addressing the theories advanced by Drs. Ferraris and Rotella was served on July 19, 2019.

For the '689 patent, Defendants argue that the patented invention would have been obvious to a POSA. Dr. Ferraris opines that the '689 patent is invalid as obvious under 35 U.S.C. § 103. (*Id.* ¶¶ 46-47.) He suggests that a POSA at the time of Takeda's invention who was trying to develop an effective DPP-IV inhibitor would have identified a single molecule (DCAX) from publications that describe hundreds of similar molecules – many that were demonstrably more effective or extensively tested – and would have selected DCAX as the lead compound for further investigation. Dr. Ferraris then contends that the POSA would have made ***multiple*** specific chemical modifications to DCAX, including changing the entire core structure via a process that he calls "scaffold hopping," in order to finally arrive at Alogliptin.

Dr. Rotella argues that the '689 patent is invalid based on the judicially-created doctrine of obviousness-type double patenting. (*Id.* ¶ 162.) According to Dr. Rotella, a POSA who considered one of the many compounds described in a prior art patent owned by Takeda, the '344 patent, would have been motivated to make ***multiple*** specific changes to that compound – again including replacement of the central core structure via "scaffold hopping" – to arrive at Alogliptin, thus making it "obvious" in view of the '344 patent.

Respectfully, Takeda submits that, even giving Defendants every benefit of the doubt, they have not presented any disputed issue of material fact that would warrant a trial in this case. Especially in light of the high burden applicable to Defendants' invalidity challenges, this matter can, and should, be decided in Takeda's favor as a matter of law and without expending the resources that a trial would demand from the parties and the Court.

III. LEGAL STANDARDS

"Summary judgment is appropriate if, viewing the evidence in the light most favorable to the non-moving party, the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." *EON Corp. IP Holdings LLC v. AT&T Mobility LLC*, 785 F.3d 616, 620 (Fed. Cir. 2015). "Because Defendants bear the burden of proof of invalidity, Plaintiffs meet their initial burden by pointing to the absence of evidence to support Defendants' invalidity case, and the summary judgment burden then shifts to Defendants." *Shire LLC*, 2014 WL 2861430, at *13 (granting summary judgment of validity because the prior art references did not disclose the claimed compound or suggest its synthesis from a lead compound). In deciding motions for summary judgment, "the Court need not credit conclusory statements by experts and need not find such statements sufficient to raise material factual disputes." *Id.* at *14.

Finally, because federal statute mandates that a "patent shall be presumed valid," 35 U.S.C. § 282(a), the burden that Defendants bear to prove their obviousness claims and overcome that presumption is the highest in civil law – "clear and convincing evidence." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).[3] Defendants' challenges are based on prior art and, where a prior-art reference is listed on the face of a patent (as is the case for Defendants' primary references), "the examiner is presumed to have considered it," and the challenger has the "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." *Shire LLC,* 802 F.3d at 1307 (internal quotations omitted). This presumption is particularly salient here, as patents are issued by "examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level

[3] This applies equally to Defendants' obviousness-type double patenting claim. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991) ("Double patenting is an affirmative defense," to be proven "by clear and convincing evidence, a heavy and unshifting burden.").

of skill in the art and whose duty it is to issue only valid patents." *Id.* (internal quotations omitted).

IV. ARGUMENT

A. There Is No Dispute That Defendants' Generic Alogliptin Products Infringe Claims 4 And 12 Of The '689 Patent

As stated above, both Torrent and Indoco have stipulated to infringement, so summary judgment in Takeda's favor on this issue is warranted. (SMF ¶¶ 39-40.)

B. There Is No Genuine Issue Of Material Fact Sufficient To Warrant A Trial On The Merits Of Defendants' Obviousness Claims

The FDA recognized that Alogliptin was a new chemical entity and there is no dispute that Alogliptin is not disclosed in any prior art references, nor is it anticipated by any single reference, explicitly or inherently. (*Id.* ¶¶ 44-45.) Defendants argue that Takeda's claims to Alogliptin would have been obvious in view of combinations of prior art that they have cherry-picked for this litigation, or in view of an earlier patent owned by Takeda. This challenge is extraordinary, as Takeda has identified only ***one*** case in which the Federal Circuit found a patent claiming a new chemical compound – such as Alogliptin – to be obvious in the 35 years of active litigation under the Hatch-Waxman Act. And in that case, the patentee ***conceded*** that the proposed compound was "actually being used as a lead compound at the time of the [drug's] invention" and that a POSA could be led to the drug via "conservative changes" to the lead compound's structure. *See Bristol-Myers*, 769 F.3d at 1345-46. Other than that one aberrant and inapt case, every obviousness challenge to a compound patent has failed, including those with arguments similar to Defendants' and for proposed lead compounds much closer to their claimed counterparts than here. *See, e.g., Yamanouchi*, 231 F.3d at 1345 ("prior art offer[ed] no suggestion to pursue the particular order of manipulating parts of the compounds"); *Eli Lilly & Co. v. Zenith/ Goldline Pharms., Inc.*, 471 F.3d 1369, 1378-9 (Fed. Cir. 2006) (obviousness rejected where proposed lead was adjacent homolog of claimed compound, but a different compound was identified in the art as "particularly active");

Eisai, 533 F.3d at 1358 (obviousness rejected where lead compound pathway required a POSA to "drop the very feature" identified as advantageous); *Daiichi Sankyo Co. Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1351 (Fed. Cir. 2010) (obviousness rejected in view of insufficient evidence a POSA would choose the proposed lead compound "over other better-studied ARBs with greater potency" and where most of the disclosed compounds shared common features different from that compound).

Defendants have not presented any argument or evidence that would justify a finding of obviousness. Their analyses are litigation-based hindsight, divorced from what is suggested by the references to a POSA pursuing the development of an efficacious treatment for diabetes (as opposed to a generic litigant searching to undermine a blocking patent).

1. Defendants Present No Genuine Issue Of Material Fact That Claims 4 And 12 Of The '689 Patent Would Have Been Obvious Under 35 U.S.C. § 103

The analysis this Court must apply to Defendants' statutory obviousness theory (offered through Dr. Ferraris) is clear: "[W]hether a new chemical compound would have been *prima facie* obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka*, 678 F.3d at 1291. The infringer must "prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select [the lead compound] from the panoply of known compounds in the prior art." *Id.* at 1292. A lead compound must be more than just "known as a compound;" it must be "a known active drug substance." *Shire*, 2014 WL 2861430, at *17.

If, and only if, there is a proper lead compound, the court turns to the second step, in which it determines whether the infringer has shown that "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed

compound with a reasonable expectation of success" – again by "clear and convincing evidence." *Otsuka*, 678 F.3d at 1292 (citations omitted); *accord Novartis Pharm. Corp. v. W. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019). "To have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (citations omitted). "Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharms. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019). Applying these same accepted and rigorous standards, the PTO did not raise any obviousness concerns during prosecution of the '689 patent, even after reviewing the two primary references relied upon by Defendants. There is no reason for this Court to reach a contrary conclusion. Defendants' § 103 obviousness challenge does not warrant a trial on the merits.[4]

(a) A POSA Would Not Have Chosen DCAX As A Lead Compound, Thus Dr. Ferraris' Theory Fails At The First Step

Dr. Ferraris argues that claims 4 and 12 of the '689 patent would have been obvious in view of two prior art references, the CA '730 patent and the WO '496 publication, in further

[4] In addressing a motion for summary judgment, the Court must draw all reasonable inferences in favor of the non-movant. Fed.R.Civ.P. 56. For purposes of this motion only, Takeda will not contest several of Defendants' assertions, even though Takeda believes that they are incorrect. For example, Defendants' experts argue that the priority date of the invention is March 15, 2004. While Takeda disagrees—the invention was reduced to practice no later than June 2003—here, a determination of validity is rendered from the perspective of a POSA as of March 15, 2004. Moreover, Defendants' POSA requires ***extraordinary*** skill in the art to apply structure-based drug design techniques, particularly in extracting key inhibitor-enzyme recognition and interactions from one class of inhibitors to design another, non-analogous class of inhibitors. For the purpose of this motion only, however, Takeda accepts this heightened skill level, and maintains that the inventions still would not have been obvious.

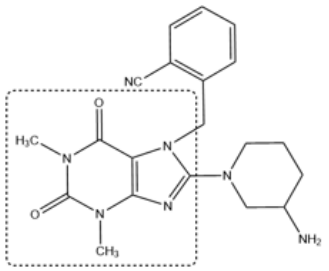
combination with one or more of over a dozen other secondary references, and then also informed by "the knowledge of one of ordinary skill in the art as of March 2004." (*Id.* ¶¶ 46-47 & Ex. 11.) Importantly, both the WO '496 publication and an equivalent of the CA '730 patent were listed on the face of the '689 patent itself as prior art, and thus considered by the PTO during its prosecution. (*Id.* ¶ 48.) The PTO allowed the claims, which it would not have done had it found that these references Defendants now rely on, alone or in combination, rendered the claimed inventions obvious.

Ignoring this important fact, Dr. Ferraris insists that the teachings of the CA '730 patent and the WO '496 publication would nonetheless have led a POSA who was endeavoring to discover a DPP-IV inhibitor as an efficacious treatment for type-2 diabetes to select a particular xanthine derivative, referred to as DCAX, as the lead compound for her analysis,[5] and then (after many, many steps allegedly suggested by numerous other prior art references) would have arrived at Alogliptin. Under established Federal Circuit precedent, this argument does not get past "go" as, first and foremost, no POSA would have been motivated to choose DCAX – the ***least potent and most different*** compound highlighted by Dr. Ferraris from a larger group of inhibitors.

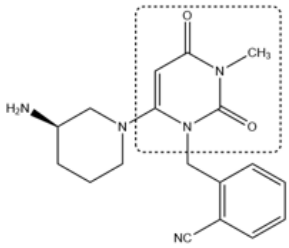
(i) DCAX And Alogliptin Are Not Analogous Structures

To begin, there is no doubt that DCAX is fundamentally different from Alogliptin. The central ring structures (also known as the "core" or "scaffold" of the molecule) of the two compounds bear no resemblance to one another (*see* dashed boxes, below):

[5] Unlike the *Bristol-Myers* case, there is no evidence that DCAX was being used or even considered as a starting point for DPP-IV inhibition to treat type-2 diabetes, or that it ever was so used or considered.



DCAX



Alogliptin

The scaffold of the DCAX compound is a purine derivative known as a xanthine (a ***double*** ringed structure in which a five-membered ring is fused to a six-membered ring), while the scaffold of the Alogliptin compound is a pyrimidine-dione (a ***single*** six-membered ring). (*Id.* ¶¶ 53-55.) The cores of the two compounds have dramatically different properties.[6] (*Id.* ¶ 56.) And it requires no fewer than six specific chemical modifications of the DCAX molecule to produce Alogliptin, hardly a "conservative change." (*Id.* ¶¶ 54-62, 107-161.) Because of these distinctions, Alogliptin is not a natural derivative of DCAX, and a POSA would have had innumerable different potential pathways to attempt to improve upon DCAX that would not have resulted in Alogliptin.

(ii) A POSA Would Not Have Chosen Xanthine-Based Compounds Over Other Known Compounds

Nothing in the literature proffered by Defendants suggests that a POSA would have selected compounds with a xanthine core as a starting point for DPP-IV inhibitors. To the contrary, Defendants' own references refute that notion. For example, Dr. Ferraris relies on a prior art article authored by Dr. Wiedeman in April 2003. (*Id.*, Ex. 17.) According to Wiedeman, prior to the time of Takeda's invention, "a number of non-peptidic molecules ha[d] been disclosed as DPP-IV inhibitors. These diverse groups of molecules include core structures such as xanthines, aminomethylisoquinolones, aminomethylisoquinolines, aminolactams and sulfonyltriazoles." (*Id.*

[6] For example, the xanthine core of DCAX is more water soluble and has a larger polar surface area relative to the pyrimidine-dione core of Alogliptin. (*Id.* ¶ 57.)

¶ 71.) Among those diverse classes of molecules, there is no dispute that several were being studied at the time. (*Id.* ¶ 72.) Yet Dr. Ferraris focuses immediately (and exclusively) on xanthine-based compounds, without any justification for why a POSA would have done so.

(iii) Nothing In The Selected References Would Have Led A POSA To Select DCAX As A Lead Compound

Even assuming (without evidence) that a POSA was somehow motivated to start with xanthine-based compounds, there is nothing to suggest that the POSA would have specifically selected DCAX as a lead compound for further development.[7] To the contrary, the very references Dr. Ferraris relies upon affirmatively teach ***away*** from DCAX.

First, DCAX is one xanthine compound among hundreds, and not a very promising one at that. The CA '730 patent alone lists more than 800 xanthine-based compounds by name and generically describes many more. (*Id.* ¶ 78.) It provides biological activity information for 31 of the more than 330 compounds that were actually synthesized, reported in terms of potency in inhibiting the DPP-IV enzyme. (*Id.* ¶ 79.) From that list, Dr. Ferraris highlights five compounds, of which DCAX (Compound 1(121)) is the ***least active***.[8] (*Id.* ¶ 82.) Thus, Defendants and Dr. Ferraris advocate not for the gold, silver or bronze medalist, but ask the Court instead to find that a POSA would have selected the ***worst performing compound*** of the group as the lead compound for further study.[9] In fact, the CA '730 patent itself identifies a sub-group of compounds as

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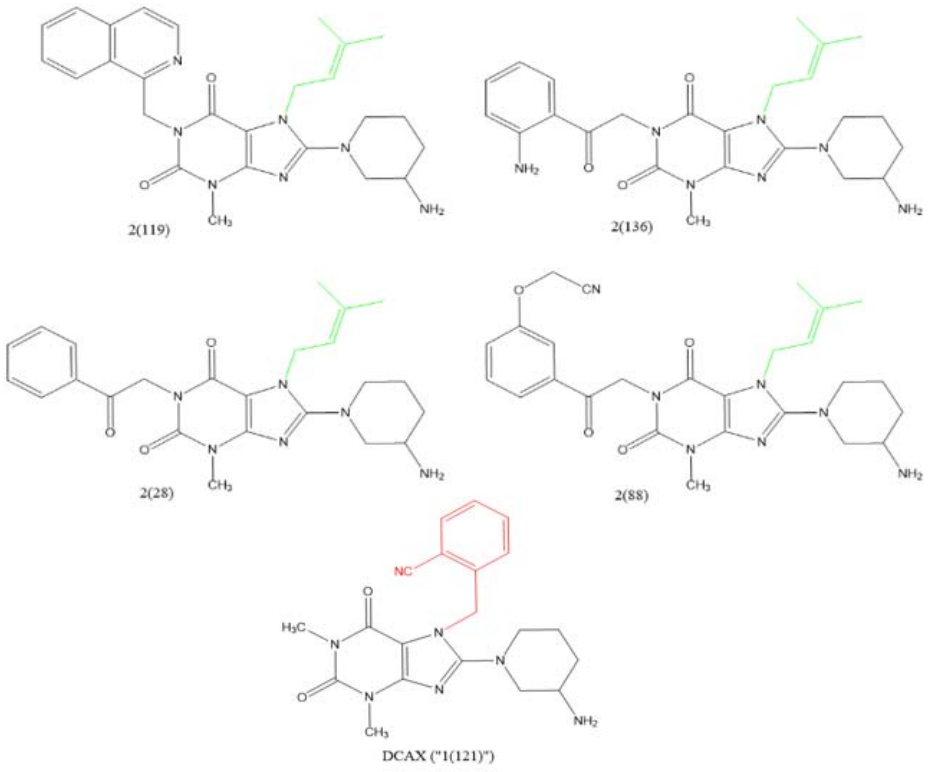
[7] Dr. Ferraris points out that DCAX is discussed in both of his hand-selected references. (*Id.* ¶ 98.) But there were at least seven other compounds that were also discussed in both references. (*Id.* ¶ 99.) And nothing about the references would make DCAX a top candidate over the others.

[8] Activity is expressed in the reference as an IC_{50} value (*i.e.*, the amount of compound needed to produce 50% inhibition of an enzyme) against DPP-IV. (*Id.* ¶ 81.) The lower the IC_{50} value, the more active (more potent) the compound is in inhibiting DPP-IV.

[9] Dr. Ferraris justifies his choice by stating that a POSA "would not discount any of the 5 selected compounds" since the difference in IC_{50} values was "negligible" (*id.* ¶83), but this further

"preferred," including the first and third most potent compounds from Dr. Ferraris' list. (*Id.* ¶¶ 84-85.) DCAX is ***not*** listed as "preferred." (*Id.*) The highlighted sub-group would have obvious relevance to a POSA, and further teaches away from the selection of DCAX as a lead compound.

Second, DCAX is structurally different from the better-performing compounds disclosed, which would have led a POSA even further away from choosing that as the lead compound. Each of the four most-potent compounds reported in the CA '730 patent (referred to as compounds 2(119), 2(136), 2(28), and 2(88)) has a methyl butenyl group at position seven of the fused bicyclic ring, shown in green in the diagram below. (*Id.* ¶ 87.) DCAX, the least-active compound in the Dr. Ferraris' highlighted group, does not. (*Id.* ¶ 88.) Instead, DCAX has a different moiety at that position, known as a "2-cyanobenzyl" group and shown in red below. (*Id.*)



demonstrates that DCAX was not an obvious lead compound. Even giving Dr. Ferraris the benefit of the doubt, a POSA would have had ***at least 5 starting points*** based on the CA '730 patent alone.

Of the 31 compounds with reported potency data, ***only*** DCAX contains a 2-cyanobenzyl group (by contrast, 25 of the tested compounds had the methyl butenyl group). (*Id.* ¶ 89.) And, of the 38 compounds that the CA '730 patent identifies as "preferred compounds," 28 have the methyl butenyl group, but ***not one*** includes a 2-cyanobenzyl group like DCAX. (*Id.* ¶ 91.) Viewing the CA '730 patent as a POSA would (as opposed to an expert trying to undermine a patent), any reasonable POSA would have inferred that compounds like DCAX containing a 2-cyanobenzyl group were not as effective as those containing the methyl butenyl group, and would not have chosen those compounds for further development. To accept Dr. Ferraris' contrary argument, one would need to believe that a POSA seeking to develop a potent DPP-IV inhibitor would have immediately ignored the extensive focus of the CA '730 patent on methyl butenyl group compounds in favor of one completely different compound that was not a top performer, and that she would do so because of the 2-cyanobenzyl group in that compound.

The authors of Defendants' own references disagree. For example, the Wiedeman reference specifically addresses the CA '730 patent, noting that it discloses "a number of very potent inhibitors." (*Id.* ¶ 101.) The "representative" "potent inhibitors" include Compound 2(136) — the second best performing compound of the 31 compounds tested — but ***not DCAX***. (*Id.*) Not surprisingly, Compound 2(136) was three times more potent than DCAX in inhibiting DPP-IV, and had the methyl butenyl group, not DCAX's 2-cyanobenzyl group. (*Id.* ¶ 80.)

Likewise, nothing in the WO '496 publication would have led a POSA to select DCAX as a lead compound. WO '496 lists more than 100 xanthine-based compounds, including DCAX, but provides no biological data at all. (*Id.* ¶¶ 94-95.) Accordingly, a POSA would have no way to know from that reference if DCAX was effective in inhibiting DPP-IV, much less how it compared to the other xanthine compounds listed. (*Id.* ¶¶ 96-97.) No information in the WO '496 publication

would, or even could, have led a POSA to pluck DCAX from the list as a lead compound.[10]

Nothing in the CA '730 patent or WO '496 publication supports the conclusion, which is the very foundation of Dr. Ferraris' obviousness theory, that a POSA would have selected DCAX as a lead compound. It was the least active of the compounds Dr. Ferraris highlighted; it was structurally dissimilar from the more potent candidates; and it was ignored in the literature at the time, which instead focused on other compounds that were better studied and/or more potent. Defendants' failure to provide any evidence (much less clear and convincing evidence) to support the selection of DCAX as a lead compound by itself warrants summary judgment for Takeda.

(b) Although The Court Need Not Reach The Second Step Of The Federal Circuit Test, Dr. Ferraris' Theories Fail There, Too

Even assuming a POSA would choose DCAX, Defendants' arguments still fail because a POSA would not have been motivated to modify DCAX in all (or any) of the ways necessary to produce Alogliptin, nor have any reasonable expectation of success in doing so. ***First***, Dr. Ferraris' theory that a POSA would modify DCAX to arrive at Alogliptin is predicated upon an unsupported assertion that a POSA would choose – via a process he calls "scaffold hopping" – to ***replace the entire core*** of the DCAX compound. "Scaffold hopping" is a theory that effective drugs may be discovered by varying the framework of a known biologically active molecule while keeping the "essential features" causing the desired activity. But central to this concept is that a POSA would ***know*** what parts of a molecule were essential and which could be modified. There is no evidence that DCAX or its analogous compounds had been studied in this manner at the time of the

[10] Again, Wiedeman is informative. Dr. Wiedeman cites to the WO '496 publication, but does not refer to DCAX. Instead, he reports that a ***different compound*** disclosed by the same research group was selected for evaluation in later studies and was considered "attractive." (*Id.* ¶ 103.) That compound was structurally very different from DCAX, and did not contain DCAX's aminopiperdinyl or 2-cyanobenzyl groups. (*Id.* ¶ 104.)

invention. (*Id.* ¶ 115.) Thus, a POSA would not know from the prior art where to begin to create a safe and effective derivative of DCAX.[11]

The "chemical arts often are unpredictable." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009). Among POSAs, it was well-known at the time of the invention that changing even a single atom in a biologically active molecule can drastically change not only its potency, but also its essential pharmacology. (SMF ¶¶ 117-18.) Thus, when changing only a single atom, it would have been impossible for a POSA to predict with certainty the characteristics that a compound would display. (*Id.* ¶ 119.) No reasonable POSA would immediately choose to make drastic modifications to a compound and expect it to demonstrate the same or improved properties. This is confirmed by the path that the actual inventors took to develop Alogliptin. In their reply expert reports, Defendants cite to a paper by Zhang, one of the inventors of the '689 patent, that describes the development efforts undertaken by his team – all of whom were unquestionably POSAs (and of the highest possible knowledge and experience). (*Id.* ¶ 124, Ex. 25.) As that reference shows, the inventors did ***not*** simply start with scaffold hopping – which they clearly would have done were this technique as obvious, effective, and risk-free as Defendants claim. (*Id.*) Instead, they were meticulous, first changing substituent groups on their lead molecules to see if they could optimize them into effective treatments. (*Id.*) That is exactly what a POSA would do, not leap straight to swapping the very core of the molecule for another.

[11] Dr. Ferraris' argument that a POSA would be motivated to use "scaffold hopping" in 2004 is based largely on the Böhm reference – one that he admits is not prior art to the invention – which itself recognizes that "serendipity has played a large role" in its few real world examples. (*Id.* ¶¶ 111-14 .) This is exactly the opposite of the required expectation of success.

Second, even if a POSA were to somehow decide to replace DCAX's core, based on Dr. Ferraris' argument, the POSA would need to take each of the following exact steps to arrive at Alogliptin ***after*** selecting DCAX and replacing its xanthine scaffold of DCAX with a uracil scaffold (despite no suggestion in the references to do so): (1) choose to retain certain DCAX substituents; (2) choose to discard other DCAX substituents; (3) choose a specific orientation of the selected groups about the new monocyclic uracil scaffold; (4) choose to add a further substituent on the resulting new molecular framework; and (5) choose a specific enantiomer of the amino group on the new molecular framework. (*Id.* ¶¶ 140-54.) And further for claim 12, (6) choose a specific, rarely utilized, benzoate salt. (*Id.*¶¶ 155-61.) None of the cited references, nor the knowledge of a POSA in March 2004, provides any teaching, suggestion, or motivation to make these choices with a reasonable expectation of success for this dramatic reconfiguration of the poorer-performing DCAX "lead compound." A reasonable POSA would not do so.

(i) A POSA Would Not Have Replaced The Xanthine Core In DCAX With A Uracil

Dr. Ferraris's references are both focused solely on compounds with xanthine scaffolds.[12] Neither reference provides any motivation to replace the fused, bicyclic xanthine scaffold of DCAX with the unfused, monocyclic uracil scaffold present in Alogliptin. (*Id.* ¶¶ 128-29.) To the contrary, these references would have discouraged it.

The focus on xanthine-based compounds in Dr. Ferraris' references would only have confirmed to a POSA that a xanthine scaffold (not a uracil) was a central, ***critical*** feature of these compounds, including DCAX. Dr. Ferraris, in fact, justifies selecting DCAX as a lead compound

[12] For example, of the more than 330 final compounds prepared in the CA '730 patent, each and every one is xanthine-based. (*Id.* ¶ 126.) The reference does not even discuss uracil scaffolds. (*Id.* ¶¶ 127.) The xanthine scaffold is also common to all of the compounds in the WO '496 publication. (*Id.* ¶ 126.)

because of "the interest in non-peptidic DPP-IV inhibitors containing a ***xanthine core***" (*Id.* ¶ 108 (emphasis added).) ***Tellingly, Dr. Ferraris does not present a single prior art that teaches or suggests replacing xanthine with uracil in developing a DPP-IV inhibitor***. (*Id.* ¶ 130.) Instead, he first argues – without support – that a POSA: (1) would want to reduce the molecular weight of a core scaffold, (2) "would have substituted one ring structure for a two ring structure in Compound 1(121) [DCAX] to see if the compound retained its potency and determine whether the two ring structure was essential", and (3) "would naturally consider replacing xanthine with other nitrogen-containing bases." (*Id.* ¶ 109.) In so arguing, Dr. Ferraris actually illustrates the countless different potential pathways available to a POSA attempting to improve upon DCAX that would not result in the claimed compound. Dr. Ferraris' approach reveals that he is merely varying all parameters and exploring all possible choices to arrive at Alogliptin.

The fused double-ringed structure of compounds like DCAX is not immediately interchangeable with the central monocyclic ring system of Alogliptin. Xanthine has different properties than uracil, such as molecular weight, total surface area, melting point, water solubility, and pK_a. (*Id.* ¶ 131.) As discussed above, it was known that changing even one atom in a molecule could alter its properties. (*Id.* ¶¶ 115-19.) Therefore, given the stark differences in the properties of these central ring structures, a POSA would have assumed that changing from xanthine to uracil would have a dramatic effect. In fact, a POSA would have understood that changing the scaffold would be the single change ***most likely*** to alter a compound's properties, and would have had no reason to presuppose that doing so would lead to a compound that was more effective, but no less safe. Fundamentally, it makes no sense that a POSA would have first discarded the central framework upon which DCAX was built to substitute an entirely different structure, particularly not when (according to Dr. Ferraris) the existing framework of DCAX was what made it attractive

in the first place. (*Id.* ¶ 108.)

Nevertheless, Dr. Ferraris digs in and suggests that a POSA would have been motivated to change to a uracil scaffold in DCAX in view of what he calls three "Substitution References." (*Id.* ¶ 132, Exs. 26-28.) Not so. First, those references have ***nothing to do with DPP-IV inhibitors***; they are directed to completely different molecular targets, such as antiviral compounds, inhibition of specific non-DPP-IV intracellular signaling events, and CDK enzyme inhibitors. (*Id.* ¶¶ 132-38.) Second, those references list xanthine and uracil only amongst a long list of potential rings that can be used for targets unrelated to DPP-IV. (*Id.*) And third, none of those references states a preference to replace xanthine with uracil, or discloses that the respective central rings of such compounds are interchangeable with any reasonable expectation of success or predictability. (*Id.*)

(ii) A POSA Would Not Have Undertaken The Necessary Remaining Selection (And Elimination) Of Substituent Groups

Even assuming that a POSA would have replaced the central xanthine ring of DCAX with a uracil, she still would only arrive at Alogliptin if she happened to also choose to retain specific groups from the original xanthine ring while removing others, as well as properly arranging each group about the uracil, yet another example of the numerous pathways a POSA could pursue that would not result in Alogliptin. (*Id.* ¶¶ 140-47.) Dr. Ferraris does not address that even one change of molecular structure by retaining or removing a certain group could significantly alter the biological activity of the molecule. A POSA would know this, and would be sensibly cautious of the potential safety and other risks inherent in making some or all of the changes required to complete Dr. Ferraris' reverse-engineering of Alogliptin.

(iii) A POSA Would Not Have Selected The Specific Stereoisomer Needed To Arrive At Alogliptin

Finally – even compounding one improbable step after another to assume that the POSA would focus on xanthine-based compounds, pick DCAX as a lead compound, switch out the

xanthine core for uracil, and then make every right call about which substituent groups attached to the xanthine ring to keep and which to discard – the POSA ***still*** could not produce Alogliptin unless she chose the correct, specific stereoisomer. (*Id.* ¶¶ 148-54.) Nothing in Dr. Ferraris' primary references teaches or suggests the need for selecting a specified stereoisomer.[13] And while Dr. Ferraris cites to five papers he calls "Stereoisomer References" for motivation, these do not provide a POSA a reason to select the specific stereoisomer for Alogliptin with any reasonable expectation of success.[14] (*Id.* ¶¶ 154.) And there would have been no such expectation, as it is difficult to predict whether a new chemical compound will have particular pharmacological properties even when analogous compounds may be known to the POSA. (*Id.* ¶ 119.)

(c) A POSA Would Not Have Made The Benzoate Salt

Salt selection, as a general rule, is considered an unpredictable art. (*Id.* ¶¶ 155-61.) The choice of salt depends on many factors, including the desired bioavailability, solubility, formulation properties and cost. (*Id.* ¶ 158.) Dr. Ferraris argues that using the benzoate salt would have been obvious and that its effectiveness would have been predictable, relying on what he calls "Salt References." (*Id.*.) But even those references plainly state that there is "no reliable way of predicting" how well a particular salt will work. (*Id.* ¶ 159.)

(d) Ultimately, Dr. Ferraris' Obviousness Argument Is Based On Nothing More Than Improper Hindsight

The tortured path that Dr. Ferraris maps, in hindsight, from xanthine-based compounds to

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[13] The CA '730 patent, for instance, includes both stereoisomers of three separate compounds among the "preferred" list, indicating no particular preference between stereoisomers. (*Id.* ¶ 152.)

[14] Dr. Ferraris argues that a POSA would be able to select the correct stereoisomer from routine experimentation. (*Id.* ¶ 151.) Even if true – and this is supported only by Dr. Ferraris' own words – it admits that further experimental pathways were necessary for a POSA to obtain Alogliptin and reinforces its non-obviousness.

DCAX to the Alogliptin compound described in claim 4 of Takeda's '689 patent would never have been obvious to a POSA. Dr. Ferraris' multi-step obviousness theory is possible only because Alogliptin is (through Takeda's efforts) now known and well characterized, allowing Dr. Ferraris to look backward and construct a path for how one could have gotten to Alogliptin from the prior art. It is a hindsight analysis, pure and simple. Nothing in Dr. Ferraris' references would have motivated a POSA to start with DCAX, nor to make any of the subsequent modifications that are critical to his obviousness theory – any ***one*** of which could have had catastrophic consequences for the safety, efficacy, and/or utility of the molecule. There was no manifest need to do these things, nor anything in the literature that suggests a POSA would have had a reasonable (indeed any) expectation of success in doing so. And, when one considers just how many other decisions a POSA could have made at each of the required steps – which would have sent her off in innumerable different directions – the idea it would have been ***obvious*** for her to have made every correct choice at every stage to reach Alogliptin (or its benzoate salt) defies credulity.

Indeed, this Court's decision in *Shire LLC v. Amneal Pharms., LLC* further confirms that the sort of reverse engineering offered by Dr. Ferraris is not sufficient to withstand summary judgment. *Id.*, 2014 WL 2861430. The defendants in *Shire* sought to invalidate patents that covered the active ingredient in Vyvanse® (lisdexamfetamine dimesylate), arguing that the claims were obvious over a single prior-art reference, AU '168, which disclosed multiple compounds and suggested their potential combination. *See Id.* at *18. In particular, AU '168 disclosed d-amphetamine, encouraged people to modify amphetamine, disclosed the possibility of combining amphetamine with a list of 18 amino acids "and the like," and expressed a preference for the L form of the amino acids. *Id.* Defendants claimed that a POSA would have derived lisdexamfetamine because the 18 amino acids disclosed were part of a "small and finite group."

Id. at *19. That was not enough, in this Court's view, to survive summary judgment. *Id.*

As the Court explained, the results of the various mixing and matching options in AU '168 were not "predictable." *Id.* The defendants "d[id] not propose a theory in which the skilled artisan has a reason to pick [the specific compound] from that group," and they "failed to explain why" the compounds "form a finite number of identified and predictable solutions" to the problem of which compounds to combine. *Id.* at *18-19. Further, the defendants "d[id] not point to anything which supports the inference that these are solutions to a particular problem, and certainly not that they are predictable." *Id.* at *19. The Federal Circuit affirmed, observing that "[n]othing in AU '168 specifically suggests combining d-amphetamine with L-lysine." *Shire*, 802 F.3d at 1307. The list of "18 amino acids 'and the like'" that can be either in D- or L-form was too general. *Id.*

Defendants and Dr. Ferraris present no better case than that found wanting in *Shire.* Indeed, it is in fundamental ways even worse. At least in *Shire*, a single reference listed all the compounds and suggested that they could be combined in some fashion. Here, by contrast, the primary references do not even provide a POSA with any reason or motivation to choose DCAX from hundreds of other disclosed compounds, much less a reason or motivation to modify DCAX in all (or any) of the ways required to reach Alogliptin. Thus, just as in *Shire*, there is only hindsight analysis, devoid of facts. And just as in *Shire*, summary judgment of no invalidity is warranted.

2. Defendants' Obviousness-Type Double Patenting Argument Similarly Does Not Warrant A Trial

Defendants' other expert, Dr. Rotella, argues that the claims of the '689 patent are invalid for obviousness-type double patenting – a legal doctrine that invalidates claims that are not patentably distinct from one or more claims in a different, earlier-expiring patent. In his opinion, claims 4 and 12 of the '689 patent are obvious over claim 162 (out of 169 total claims) of the '344 patent in view of Kim 1998 and whatever "common knowledge" was available to a POSA as of

March 2004. (*Id.* ¶ 162.) Like Dr. Ferraris, Dr. Rotella's pathway to Alogliptin involves a series of improbable steps that the PTO did not take and that no rational POSA would take.

To analyze obviousness-type double patenting, a court must first "construe[] the claims in the earlier patent and the claims in the later patent and determine[] the differences." *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1323 (Fed. Cir. 2018) (internal quotations omitted). "The question, thus, is whether the later invention is a '***slight variant***' of the earlier." *Pfizer, Inc. v. Teva Pharms. USA. Inc.*, 803 F.Supp.2d 409, 448 (E.D. Va. 2011) (emphasis added) (citing *Geneva Pharms, Inc. v. GlaxoSmithKline P.L.C.*, 349 F.3d 1373, 1378 (Fed. Cir. 2003)). The "differences" between the prior art and the claimed invention "cannot be considered in isolation—the claims must be considered as a whole." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1377 (Fed. Cir. 2012).

The second part of the analysis is "analogous to the obviousness inquiry under 35 U.S.C. § 103." *UCB*, 890 F.3d at 1323. It "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." *See Eli Lilly*, 689 F.3d at 1378 (rejecting obviousness-type double patenting where the proposed modification was not proved to be "the one, among all the possibilities, that would have been successfully pursued" given the many "opportunities for modification"). Indeed, "[t]here is no other way to consider the obviousness of a compound B over compound A without considering whether [a POSA] would have had reason to modify A to make B." *Otsuka*, 678 F.3d at 1298. Even compounds that differ only slightly in structure may not be obvious variants. *See*, *e.g.*, *Eli Lilly*, 689 F.3d at 1377 (difference in ring structure, but same substituents); *Bayer AG v. Dr. Reddy's Labs., Ltd.*, 518 F.Supp.2d 617 (D. Del. 2007) (rejecting claim even where "[t]he only difference between" the claims was "the 8-position substituent").

As discussed below, Dr. Rotella not only papers over the significant differences between claim 162 and Alogliptin, but he also fails to provide any reason why a POSA would be motivated to modify claim 162 at all (and certainly not in all the ways necessary to reach Alogliptin). There is no evidence – much less clear and convincing evidence – that a POSA looking to make a safe and effective DPP-IV inhibitor and seeing claim 162 would take all of the steps necessary to arrive at Alogliptin with a reasonable expectation of success.

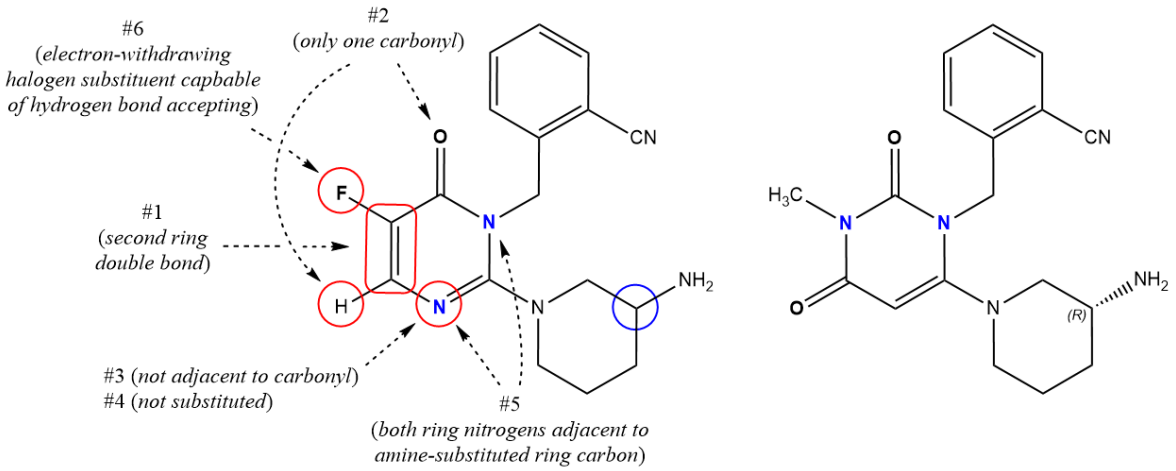
(a) Alogliptin And Its Benzoate Salt Are Significantly Different From Claim 162 Of The '344 Patent

The '344 patent is directed to pyrimidinone-based compounds for use as DPP-IV inhibitors. (*Id.* ¶ 165, Ex. 33.)[15] Each of the final compounds prepared in the '344 patent, including that of claim 162, is a multi-ring compound where the central ring system is a pyrimidinone ring. (*Id.* ¶ 166.) It is undisputed that Alogliptin is not disclosed or contemplated in the '344 patent. (*Id.* ¶ 170.)

Claim 162 itself is directed to a specific compound,[16] not a broad genus of compounds. (*Id.* ¶ 169.) The claim 162 compound and Alogliptin are not "slight variants" – there are several, significant differences between them:

[15] The '344 patent is not related to the '689 patent, but the publication that resulted in the '344 patent was cited on the face of the '689 patent. (*Id.* ¶ 164.)

[16] Claim 162 further does not specify a stereoisomer (circled in blue, below). (*Id.* ¶ 169.) Dr. Rotella argues that this is a clerical error that a POSA would overlook. For the purposes of this motion only, Takeda agrees the Court should accept Dr. Rotella's view, consistent with the summary judgment standard.



Claim 162 of the '344 patent **Alogliptin**

For example, there are different configurations of the central ring nitrogen atoms (marked in blue) and carbon atoms, different single and double bond arrangements (boxed in red), and the compound of claim 162 includes a halogen substituent (fluorine, F, circled in red) and a hydrogen substituent (H, circled in red) adjacent to each other. (*Id.* ¶¶ 171-75.) A POSA would recognize at least the following structural differences, shown in the diagram above, as significant, but would not have been able to predict the effect of any or all of these differences on safety or efficacy:

	Central ring compound of claim 162	**Central ring Alogliptin**
(1)	two ring double bonds	one ring double bond
(2)	one carbonyl	two carbonyls
(3)	only one of two ring nitrogens adjacent to a carbonyl	both ring nitrogens adjacent to at least one carbonyl
(4)	one of two ring nitrogens substituted with a pendant group	both ring nitrogens substituted with pendant groups;
(5)	both ring nitrogens adjacent to the amine-substituted ring carbon	only one ring nitrogen adjacent to the amine-substituted ring carbon
(6)	ring *carbon* substituted with an electron-withdrawing substituent capable of forming hydrogen bonds as a hydrogen-bond acceptor (*i.e.*, a fluorine atom)	ring *nitrogen* substituted with a hydrophobic, and mildly electron-donating substituent that is unable to form hydrogen bonds (*i.e.*, a methyl group)

Every single compound in the '344 patent has differences (1) through (5), reflecting the fact that those five elements were central to the invention of claim 162. (*Id.* ¶ 176.) And six of the 36 compounds exemplified in the '344 patent had difference (6), indicating a particular interest in the fluorine substituent. (*Id.* ¶ 177.) Thus, it would ***not*** have been obvious to a POSA to change those elements of the '344 patent, as Dr. Rotella's theory would require.

(b) A POSA Would Have No Reason To Modify Claim 162 To Reach Alogliptin With Any Reasonable Expectation Of Success

Dr. Rotella ignores the unquestionable differences between the compounds to argue that a "simple" "two-step" scaffold replacement of the pyrimidinone in claim 162 to the pyrimidine-dione ring system of uracil would lead a POSA to Alogliptin. (*Id.* ¶ 179.) He proposes that a POSA would be motivated to do this in two ways – by viewing Kim 1998 and by the "common knowledge in the art" that a fluoro-olefin mimics an amide bond in DPP-IV inhibitors. (*Id.* ¶ 162, 211.) Both of these arguments fail for multiple reasons.

Before even considering whether replacing the compound's central core from a pyrimidinone to uracil would have been obvious, Dr. Rotella's stated motivation for a POSA to make ***any changes at all*** lacks critical evidence. Nothing in the '344 patent suggests that the claim 162 compound is anything but a potent DPP-IV inhibitor; Dr. Rotella points to no motivation to change it.[17] (*Id.* ¶ 178.) Further, even if there were a basis to optimize the claim 162 compound, a POSA would first choose to alter substituents to improve upon potency, selectivity, or other beneficial features. Instead of this conservative and logical first step, Dr. Rotella insists that a

[17] The '344 patent did not report specific potency data against the DPP-IV enzyme for any of the prepared compounds, but stated "the apparent inhibition constants (K_i) for compounds of the ['344 patent], against DPP-IV, were in the range from about 10^{-9} M to about 10^{-5} M." (*See* the '344 patent at col. 101, lines 23-31). Thus, a POSA would have no reason from the disclosure to "optimize only the pyrimidinone core," nor would she have any understanding of the alleged benefits Dr. Rotella's strategies would provide to the eventual compound.

POSA would view claim 162 and immediately decide to alter the core of the compound. And, he further asserts that a POSA would make this leap ***assuming*** the scaffold change would improve potency with no negative effects on biological or chemical features. These arguments fail for the same reason as discussed above in Part IV.B.1.

Even if scaffold hopping were the logical first step (it is not), Dr. Rotella fails to establish why a POSA would immediately choose uracil to the exclusion of all other potential scaffolds with any reasonable expectation of success. Uracil cores are not disclosed as a potential substitute – or for any other reason – in the '344 patent. (*Id.* ¶ 189.) A myriad of other changes could have been made to this complex compound. Dr. Rotella's selection of a switch to a uracil core is pure hindsight. *See Eli Lilly*, 689 F.3d at 1378.

Dr. Rotella first argues that a POSA would replace the pyrimidinone-based scaffold with uracil because the uracil compound itself was described in Kim 1998 as having anti-diabetic activity.[18] (SMF ¶ 190, Ex. 34.) This is incorrect. Dr. Rotella admits that Kim 1998 makes ***no mention*** of the DPP-IV enzyme or even explicitly discusses type 2 diabetes. (*Id.* ¶ 191.) A POSA looking to develop potent DPP-IV inhibitors simply would not identify, much less look to, Kim 1998 for any guidance whatsoever.

[18] Dr. Rotella also argues a POSA would create a model from co-crystal structures of DPP-IV enzyme with peptidic DPP-IV inhibitors that bind to its active site, screen databases of "all DPP-IV inhibitors and small molecules that were known to bind DPP-IV," and after iterative evaluations and further modifications of potential compounds, *i.e.*, "computer-aided scaffold replacement and fragment-based screening," eventually identify a potent, selective DPP-IV inhibitor. (SMF ¶183.) Even assuming for this motion that a POSA at the time would have the skills to perform this task, this extensive, iterative process is a research program, not a reason or motivation that would have only (or primarily) led a POSA from claim 162 compound to Alogliptin with any reasonable expectation of success. This is hardly the hallmark of a "slight variant."

Indeed, Kim 1998 does not disclose whether uracil inhibits the DPP-IV enzyme, or even whether uracil's anti-diabetic activity is related to DPP-IV activity or is specific for type II diabetes. (*Id.* ¶ 192.) And Kim 1998 does not suggest that uracil would have been particularly promising in treating diabetes among the compounds tested. (*Id.* ¶ 193.) Even if a POSA were to review Kim 1998, she would not conclude that uracil was a potent inhibitor of blood glucose. Kim 1998 reports that the compound "Rutin" had the highest total inhibition. (*Id.* ¶ 194.) Uracil, by contrast, scored on par with ascorbic acid (Vitamin C) in terms of blood glucose inhibition rates (18.3% versus 18.1%), which would not have made uracil stand out for further development. *(Id.)* Thus, Defendants' identification and reliance on Kim 1998 is pure hindsight.[19]

In contrast to Kim 1998, Wiedeman describes multiple classes of known DPP-IV enzyme inhibitors that may be useful in treating type II diabetes – and does not mention uracil among them. (*Id.* ¶ 195.) Similarly, other references identified more promising anti-diabetes compounds that had been evaluated in controlled clinical trials. (*Id.* ¶ 196.) Dr. Rotella does not provide any reason or motivation for a POSA to ignore the better-studied compounds and instead combine the claim 162 compound with untested uracil from Kim 1998 (which, again, is not directed to DPP-IV inhibition) to make a drug to combat diabetes.

Perhaps recognizing that Kim 1998 cannot bear the required weight, Dr. Rotella presents an ***alternative*** argument based on switching out groups having chemical or physically (*e.g.*, size, shape, and 3D-orientation) similar features. (*Id.* ¶ 211.) The claim 162 compound includes a

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[19] Even assuming a POSA were to take the improbable step of replacing the core of the claim 162 compound with uracil, and further assuming she would also pick the exact substituents Dr. Rotella requires to be ***retained*** (2-cyanobenzyl and aminopiperidinyl), ***removed*** (fluorine), and then ***added*** (methyl), the resulting combinations ***still*** result in 4 potential compounds, only one of which is Alogliptin. (*Id.* ¶¶ 198-209.) Dr. Rotella provides no principled justification for his litigation-based hindsight selection of only Alogliptin, much less why the other three possibilities would necessarily be eliminated.

group known as a fluoro-olefin, while Alogliptin includes an amide, and Dr. Rotella tries to justify swapping those two groups. He posits that, because amide groups were sometimes replaced with fluoro-olefin groups in the development of prior DPP-IV inhibitors, a POSA looking at the claim 162 compound would be motivated to do the ***exact opposite*** and replace the fluoro-olefin in that compound with an amide. (*Id.* ¶ 212.) Dr. Rotella asserts this theory because the groups share similar chemical and physical features, but he provides no reason ***why*** a POSA would do this; to the contrary, every example he cites runs in one, and only one, direction –introducing a fluoro-olefin group to replace an amide. (*Id.* ¶ 213.) Moreover, the prior art replacements were all made to address biological instabilities observed in amide containing compounds by providing a more stable fluoro-olefin group. (*Id.* ¶ 214.) Dr Rotella points to no similar observed issues with the claim 162 compound that would have motivated a POSA to go against the cited art to switch to the amide. (*Id.*) Further, modification of a compound with groups like an amide can impact the "size, shape, electronic distribution, lipid solubility, water solubility, pK_a, chemical reactivity, and hydrogen bonding." (*Id.* ¶ 214.) In litigation, Dr. Rotella ignores this; in the laboratory, a POSA would not.

Moreover, even assuming a POSA would be motivated to swap a fluoro-olefin group for an amide (she would not), Dr Rotella's theory still fails as it further requires a POSA to spatially orient the replacing amide group so that its features ***no longer match*** those of the fluoro-olefin group in the claim 162 compound – chemically or physically. (*Id.* ¶ 216-18.) Any POSA attempting such a switch would seek to replace the relevant chemical group in the former with its counterpart so their chemical or physically similar features matched. (*Id.*) But, once again, Dr. Rotella's theory requires the POSA to do ***the opposite***, flipping the orientation of the replacing group (and its features), and thereby disregarding his underlying premise that a POSA would

replace groups having similar features. (*Id.*) While Dr. Rotella presumes – without support – that a POSA would try both methods (the normal way (matched) and his opposite way (mismatched)), ***neither*** would get a POSA to Alogliptin.[20] (*Id.*) And even if a POSA were to perform this experimentation, Dr. Rotella offers nothing to show that she would have had a reasonable expectation of success with either route. Just like his theory based on Kim 1998, Dr. Rotella's fluoro-olefin substitution theory is a fanciful, hindsight analysis drawn to fit a litigation position. It is not science.

V. CONCLUSION

For these reasons, Takeda respectfully requests that the Court enter summary judgment that Claims 4 and 12 of Takeda's U.S. Patent No. 7,807,689 are infringed and not invalid, consistent with the proposed order that Takeda submits with this motion.

[20] Dr. Rotella's mismatched way also relies on Kim 1998 to replace the resulting compound's scaffold with uracil, which fails for the reasons discussed above. Moreover, even assuming a POSA would have replaced the core of the claim 162 compound with uracil through either of Dr. Rotella's proposed theories, he again provides no reason why a POSA following such a modification would then pursue all (or any) of the remaining steps needed to reach Alogliptin or its benzoate salt. (*Id.* ¶¶ 198-209.) Those steps are similar to those posited by Dr. Ferraris, and fail for the same reasons. (*See* Part IV.B.1, *supra*.)

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